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Population pharmacokinetics of piperazine in young Ugandan children treated with dihydroartemisinin-piperazine for uncomplicated malaria

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Abstract

This prospective trial investigated the population pharmacokinetics of piperazine, given with dihydroartemisinin to treat uncomplicated malaria in 107 Ugandan children 6 months to 2 years old, an age group previously unstudied. Current weight-based dosing does not adequately address physiological changes in early childhood. Patients were administered standard three-day oral doses and provided 1,282 capillary plasma concentrations from 218 malaria episodes. Less than 30% of treatments achieved 57 ng/mL on day 7. A three-compartment model with first-order absorption described the data well. Age had a statistically significant effect ($p < 0.005$) on clearance/bioavailability in a model that accounts for allometric scaling. Simulations demonstrated that higher doses in all children, but especially in those with lower weight for age, are required for

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Conflict of interest

The authors have no conflicts of interest to disclose.

Author Contributions

N.C.S. and S.P. wrote the manuscript; N.C.S., L.Y., F.A. and S.P. analyzed the data; D.J. C., S.M., E.A., V.B., H.W., and A.K. performed the research; F.T.A. and S.P. oversaw the research study; J.T. and F.N. assisted in study design; N.L. performed the sample analysis; J.W.T. oversaw the conduct of the parent study. All authors contributed to editing the manuscript.

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adequate piperazine exposure, though safety and tolerance will need to be established. These findings support other evidence that both weight and age-specific guidelines for piperazine dosing in children are urgently needed.

Keywords

malaria; population pharmacokinetics; piperazine; antimalarial; pediatrics; children; artemisinin combination therapy; NONMEM

Introduction

Malaria remains among the most significant causes of morbidity and mortality in the developing world. Those most at risk are children less than five years of age and pregnant women, predominantly in sub-Saharan Africa. Currently, the World Health Organization (WHO) recommends artemisinin-based combination therapies (ACTs) as first-line treatment for uncomplicated *Plasmodium falciparum* malaria in all risk groups, except during the 1st trimester of pregnancy. (1) Dihydroartemisinin-piperazine (DP) is among the most effective ACT regimens, all of which combine a short-acting artemisinin derivative with a long-acting partner drug, in this case, piperazine (PQ).

While artemisinin is more potent for reducing parasite burden, PQ protects against recrudescence malaria, emergence of parasites with reduced artemisinin sensitivity, and extends the period of post-treatment protection against recurrent infection due to its prolonged duration in the body. (2) PQ has amongst the longest terminal half-lives of currently used partner drugs, approximately 23 days in children 2–10 years of age. (3) In a mixed population of adults and children 3 years of age and older, all of whom had malaria, the mean terminal half-life of PQ was reported to be 28 days (4) and in healthy subjects given a single 500 mg to 1500 mg dose, it ranged from 11–18 days. (5)

Few pharmacokinetic (PK) studies have been published for ACT regimens in young children from sub-Saharan Africa (3) or elsewhere, (6, 7, 8) and none specifically study DP in children under 2 years of age. Currently recommended doses of DP to treat malaria in young children were chosen by scaling adult doses based on weight, with the implied target of a similar plasma concentration-time profile. (1, 9) Such an approach does not adequately address physiological changes inherent to early childhood that affect PK, such as maturation of hepatic and gastrointestinal isoenzymes and altered distribution. (10) Even with developmental considerations, PK predictions in children are imperfect and require re-evaluation once clinical data become available. In anticipation that millions of doses of DP are likely to be administered yearly as treatment or for prevention, (11, 12) it is critical to understand the PK of PQ so that its use can be optimized, particularly in those most at risk of disease. Using a population PK approach (13) coupled with small volume capillary plasma sampling for drug levels, (14, 15) we undertook a prospective population PK study of PQ in children aged 6 months to 2 years in the high transmission area of Tororo, Uganda.

Results

Population Pharmacokinetics

Participants in this PK were part of a larger malaria treatment trial in Uganda. (16) Blood samples for PK analysis were collected in 107 patients during each of 218 episodes of malaria treatment. Covariates were measured on the first treatment day of each occasion, with the exception of vomiting which was assessed during the first three days. Continuous covariate values, reported as the median of the individuals' means across treatments (and range) are as follows: age 445 (206 to 693) days; body weight 9.0 (5.1 to 12.5) kg; hemoglobin 10.0 (5.6 to 14.7) g/dL; baseline parasite density 45,126 (32 to 322,560) parasites/mL; and height-for-age z-score -2.2 (-5.8 to 0.6). The occurrence of each categorical covariate that was assessed is as follows: female (n=43); breast fed during at least one occasion (n=50); vomiting in association with drug administration during at least one occasion (n=25); trimethoprim-sulfamethoxazole (TS) use during at least one occasion (n=41); HIV infected status (n=12); and antiretroviral therapy (ART) use (n=10).

In total, there were 1,282 evaluable capillary plasma concentrations at the following nominal times: day 0 (baseline) (n=118); pre- and post-last dose, which occurred on day 2 (n=212); day 3 (24-hour post-last dose) (n=213); day 7 (n=208); day 14 (n=217); day 21 (n=196); and day 28 (26 days post-last dose) (n=118). Figure 1 shows the individual plasma concentration-time curves of PQ for all children in the study. The number of concentration-time points from each occasion is as follows: 1st=571; 2nd=471; 3rd=214 and 4th=26. Three additional samples were excluded from the analysis because they were below the limit of quantification.

The PQ plasma-concentration time data were well described with a three-compartment open model with first-order absorption. This model resulted in a better fit than a two-compartment model, both with and without the inclusion of covariates ($p<0.0001$ in each instance). The addition of an absorption lag time, with a point estimate of 0.32 h, was marginally statistically significant ($p=0.0074$, with 'significance' level predefined as $p=0.005$), but resulted in instability of the convergence of parameter estimation and was not retained in the model. Given the finding of "multiple peaks" seen in some individuals, we attempted to incorporate enterohepatic recirculation into the model. There was no evidence that enterohepatic recirculation accounted for these peaks (results not shown), though the sensitivity of our analysis was limited by the fact that this was a multi-dose study of an orally administered drug.

The covariate body weight was included unconditionally in the model for each of the three clearance parameters by multiplying each parameter by $(\text{weight}/\text{reference weight})^{0.75}$, and in each of the three volume of distribution parameters by multiplying each parameter by $(\text{weight}/\text{reference weight})$. The reference weight was approximately that of a one year old in this study population, 8.36 kg. Upon singular deletion of each allometric term, the objective function value (OFV) either decreased (though not statistically significantly), or increased, indicating their inclusion did not worsen the goodness of fit (GOF).

An age effect on clearance/bioavailability (CL/F), was the only statistically significant covariate effect identified ($p < 0.002$). The effect of age on F only (i.e., in the absence of age effect on CL/F) was marginally significant ($p = 0.0076$). The goodness of fit with the combination of age effect on both CL/F and F was not significantly improved compared to that with its incorporation in either CL/F alone ($p = 0.20$) or F alone ($p = 0.034$). Alternative forms of the model of age effect on CL/F that were tested included a linear model [e.g., $\theta_x \cdot (1 - \text{AGE}/\text{reference AGE} \cdot \theta_y)$] and a model with first-order change as a function of time [e.g., $\theta_x \cdot (1 - e^{-\theta_y \cdot \text{AGE}})$], but they did not have a lower OFV relative to a nonlinear model (below). No other covariates were identified as having a significant influence on any clearance or volume of distribution parameter.

The final model for the typical value (indicated by the tilde) of CL/F is as follows:

$$(\tilde{CL}/F)_i [\text{L/h}] = 6.39 \cdot (\text{WT}_i / 8.36)^{0.75} \cdot (\text{AGE}_i / 12)^{0.35}, \quad (\text{Equation 1})$$

in which AGE_i is the age (month), and WT_i the body weight (kg), of the i^{th} child. Age was centered at 12 months, and weight at 8.36 kg (the approximately median value of a 1 year old in this population), for ease of interpretation. Figure 2 shows the relationship of CL/F with both body weight and age. The terminal $t_{1/2}$, calculated from the primary parameters, was 31 days. Based on Equation 1, the predicted CL/F for the typical child 6 months of age is 4.4 L/h, for 1 year it is 6.4 L/h, and for 2 years 9.8 L/h. The corresponding weight-adjusted CL/F for a typical 1 year old is 0.76 L/h/kg. The estimates of all parameters in the final model are provided in Table 1.

A full covariance matrix for inter-individual variability (IIV) was modelled, using an exponential form of the model for each PK parameter. The estimates of the diagonal elements only are reported in Table 1. Inter-occasion (among treatments within a patient) variability (IOV) of F and CL were both statistically significant ($p < 0.0001$) and each estimated to be approximately 22%. Covariate hypothesis testing was performed with both IIV and IOV included in the model. The residual error, modelled as exponential (implemented by addition of a single additive error term to the log-transformed data), was estimated to be 61% (95% CI 59, 63%).

Figure 3 shows the goodness of fit (GOF) of the final model (with age effect on CL/F). A visual predictive check (Figure 4), shows good performance of the final model, with the median predictions falling in the middle of the data, and approximately 10% of the data falling outside the 90% prediction interval. The numerical predictive check likewise showed good predictive performance, with 51.7% (95% CI 44.9, 54.9%) of observed data points below the 0% prediction interval (PI), 2.5% (95% CI 1.3, 3.8%) below the 95% PI and 2.4% (95% CI 1.4, 3.7%) above the 95% PI.

Simulations of alternative regimens

With both age and weight as predictors of CL/F , simulations were performed to determine the proportion of treatments in the following three subgroups of (hypothetical) patients that are predicted to have various day 7, as well as maximum, capillary plasma concentrations

with alternative dosage regimens: A) 6 month–1 year (weight <10.5 kg), B) 1–2 years (weight < 10.5 kg), and C) 1–2 years (weight ≥ 10.5 kg) (Figure 5). PK data for one thousand children in each age-weight subgroup, on three occasions each, were simulated. The ages were chosen randomly from a uniform distribution. The body weights were simulated as a function of those ages, based on the following model of weight that was determined from the original data set:

$$(W\tilde{T})_i[\text{kg}] = (2.59 \cdot (\text{AGE}_i/12)^{0.981} + 5.65) * e^{(\eta_{1,i} + \eta_{2,i})}, \quad (\text{Equation 2})$$

in which $\eta_{1,i}$ represents random variability between patients, and has a variance estimate of 0.023; $\eta_{2,i}$ represents random variability within patients, and has a variance estimate of 0.00173. We chose to use this model to obtain hypothetical weights, rather than derive from a published formula or chart, because of the unique population that is represented by the patients in this trial.

The currently recommended regimens served as references to the tested alternatives: 1.5 times the current regimen and 2 times the current regimen. The percentages of simulated treatments with a predicted day 7 target of 57 ng/mL are shown in Table 2 and denoted in Figure 5. This putative target was chosen because it is the value of capillary plasma concentration that corresponds to 30 ng/mL of venous plasma concentration (17), a level previously associated with a reduced rate of recrudescence malaria. (18)

With the current regimen, fewer than 40% of children in group A, 20% in group B, and 30% in group C are predicted to have a capillary plasma concentration on day 7 of at least 57 ng/mL. The simulations indicate that, in order for 50% of children to achieve a day 7 concentration of 57 ng/mL, a dose of at least 1.5 times the reference is needed in groups A and C, but at least 2 times the reference dose is needed for group B (1–2 year old children with weight < 10.5 kg). Given concerns regarding cardiotoxicity of PQ, particularly QT prolongation, (19, 20) we also report the distribution of maximum capillary plasma concentrations (C_{max}) with each of the regimens simulated, and denote the 75 percentile, 95 percentile and highest value in each group (Figure 5). The highest C_{max} values predicted (with the highest doses tested) were approximately 3500 ng/mL, 3600 ng/mL and 3000 ng/mL, for groups A, B and C, respectively.

Discussion

This study is the largest and amongst the first to report the PK of PQ in children less than 2 years of age. Although a number of studies have been conducted in adults (4, 6, 21) and older children (3, 6, 7, 8, 14) with malaria, it is difficult to compare results of the present study to these prior studies because of important differences in trial design. One similarly designed study of 2–10 year olds in Burkina Faso, by some of the same investigators as in this study, (3) was the first to report the PK of DP in children living in sub-Saharan Africa. Both studies used the same drug product, dosing regimen, biologic fluid assayed (capillary plasma), assay and importantly, long duration of sample collection, and were able to get a stable fit of a three-compartment open model to the PK data. The long estimated terminal

$t_{1/2}$ of approximately 1 month in our study compares to the estimate of 23 days in the 2–10 year olds and is due primarily to the large peripheral volumes of distribution, approximately 722 L for one peripheral compartment, and 3990 L for the second peripheral compartment, in the typical one year old (approximate weight 8.4 kg).

Other PK studies of PQ reported more than one peak and Roshammar and colleague equated it to absorption pattern (5, 22). These investigators did not use the same product as in this study, suggesting that the phenomenon has more to do with the drug than the formulation. Another possible explanation for a second peak in a portion of patient-treatments is that it represents a shift in drug distribution, because when it occurs, it generally appears a week or more after dosing.

The most notable finding in our trial of young children is that age as well as body weight is a predictor of CL/F , with CL/F increasing as age increases. While allometric scaling takes into account differences in body size, it does not account for maturation of enzymes responsible for drug metabolism (10). Preliminary studies suggest that PQ is primarily metabolized by cytochrome p450 3A4 (CYP3A4), (23) which has the greatest change between 0 and 2 years of age. (24, 25) In this current trial, 25% of study participants were mildly underweight and 13% were moderate-severely underweight. (26) Focusing strictly on average weights, the mean weight of a 12-month old Ugandan in our study was 8.0 kg, compared to 9.3 kg from the 2009 international WHO chart. (27) Our data suggest that the enzymes responsible for PQ metabolism mature chronologically despite weight being less than “normal.” The ability to identify an effect of age on CL/F , independent of weight, may have been enhanced in this study due to the fact that these two covariates were not strongly correlated (r^2 of 0.21) in this trial.

As this study was not designed to specifically discern covariate effects on CL versus F (both of which directly influence average plasma concentration), we are unable to determine through modelling whether the effects of age are predominantly on CL , F or both. Further complicating the picture is that CYP3A4 in the gut wall decreases F (and thereby increase CL/F), and gut CYP3A4 is also subject to developmental changes. (28) ARVs were not identified as interacting with PQ, though the ARV in this study most likely to affect CYP3A4, nevirapine, is only a mild-modest inducer. (29) Additionally, there is low power to detect a drug interaction because only 10 patients were taking an ART concurrently.

It is important that the PK model for PQ not be extrapolated beyond the limits of the population we studied. The GOF of an alternative model for the effect of age on CL/F , in which weight-adjusted CL/F increases with age in a first-order manner, could not be distinguished from the final model (Equation 2) on the basis of OFV; this model suggests that the time for half of the full age effect occurs at approximately 6 months, 75% at 12 months, 87.5% at 18 months and the age effect virtually complete by 2 years of age. This result is consistent with the lack of age effect in the aforementioned study in Burkina Faso in 2–10 year olds. (3)

What is apparent in both the actual and simulated data is that 1–2 year olds who receive lower doses because their weight is below 10.5 kg have lower exposure compared to

children who are the same age, but weigh more and receive a higher dose. That is, our analysis suggests we are presently underdosing 1 to 2 year olds with lower weight (<10.5 kg) compared to those with weights >10.5 kg. In fact, based on the target exposure on day 7 believed to be “protective” against recurrent malaria, we are underdosing *all* 3 groups of children with the currently recommended dosing regimens (those used in this trial). While additional comparisons of our levels to venous levels reported in other studies could be informative, we have concentrated our assessments on day 7 comparisons, as these correlations have been best defined in the literature. It should be noted that in our study day 7 concentration was only weakly correlated with AUC ($r^2=0.11$). It would not be surprising then, if another marker were found to be better correlated with outcome.

The simulations for the reference doses reasonably matched the data (Table 2), though the simulations tended to have more individuals reaching 57 ng/mL on day 7 in the 6 to 12 month age group than is reflected in the actual data. The main reason for this disparity is because the population in the simulation was distributed uniformly within each age group, whereas the observed patients in group A tended to be comparatively older (mean age 314 days versus 272 days), though the weights were similar (both about 7.8 kg).

These finding of underdosing in young children are consistent with the Burkina Faso study of 2 to 10 years old, in which exposure to PQ was lower in younger than older children and adults even though the mg/kg dose was higher; these findings resulted in recommendations for a revised weight-based dosing scheme (3). With standard allometric scaling of WT raised to a power of 0.75 multiplied by some constant, it can be predicted by mathematics alone that smaller size individuals have a higher weight adjusted *CL*, and therefore a higher mg/kg dose requirement, than larger individuals. Our findings expand this to suggest that age is another important variable for PK in the children less than 2 years of age.

Additional support for a pressing need to re-evaluate DP dosing in children is provided by a recent report from the Worldwide Antimalarial Resistance Network (WWARN). (30) Their pooled analysis of 26 studies found that risk factors predictive of recrudescence included mg/kg dose of PQ as well as age being between of 1–5 years. PK was not available in most studies and was not included in their analysis. While their age finding may be related to non-PK factors such as immunity, our study suggests it could also be related to developmental influences of drug disposition beyond body size.

In re-evaluating dosing in young children we must bear in mind that increasing the dose, especially without spreading dosage administration over more time, may increase the risk of toxicity due to higher C_{max} values. Concerns have been raised about potential prolongation of the QTc interval with PQ, particularly its peak concentrations. (19) More recently, a study of PQ in adults in the setting of preventive administration was halted due to QTc prolongation, which was subsequently shown to correlate with C_{max} levels. (20) Although the risk of QTc interval prolongation remains low, any dosage modifications must take this risk, and general tolerability, into consideration.

In summary, this population pharmacokinetic study of piperazine in Ugandan children 6 month to 2 years of age confirms and extends the finding that children in the youngest age

group have lower systemic drug exposure than older children and adults, supporting the urgent need for dosing guidelines that consider both weight and age of young children. (3, 30, 31) Our simulations show that increasing the doses of piperaquine by at least 50% (i.e., from 160 mg to 240 mg for children 6 month to 1 year old, and from 240 to 360 mg in children 1 to 2 years old) may be required to achieve concentrations capable of “reducing risk” of recurrent infection in most patients. Because the dose of low weight (less than 10.5 kg) 1 to 2 year old children has not, in the past, accounted for an age effect in CL/F (because it has been based on weight alone), their doses should be increased even further. Though the safety profile of piperaquine is excellent, (31, 32) the impact of higher doses on safety and tolerance in these patients must be considered.

Methods

Study area and population

All parents or guardians provided written informed consent, and ethical approval was obtained from the Uganda National Council of Science and Technology, the Makerere University Research and Ethics Committee, the University of California San Francisco Committee on Human Research (#10-01881), and the Centers for Disease Control and Prevention Global AIDS Program (#5145.0). Participants in this PK study were part of a larger clinical trial in Tororo, Uganda, comparing the efficacy of artemether/ lumefantrine (AL), the 1st line treatment for uncomplicated *P. falciparum* malaria in Uganda, to DP in very young children. (31) Daily TS and triple ART with nevirapine, lamivudine and either stavudine or zidovudine were given to all HIV-infected participants, and TS alone to designated HIV-exposed participants of HIV-infected mothers until completion of breast-feeding, as per Ugandan Ministry of Health guidelines.

Children were required to be between 6 months and 2 years of age at the start of treatment for a given episode of malaria and could be studied on multiple treatment occasions. Enrolment in the PK study began on 5th June, 2008, and continued until 24th October 2008.

Treatment Regimen

DP (Duo-Cotecxin®, Holley-Cotec Pharmaceuticals) was administered as three daily doses according to total body weight at the time of diagnosis to achieve target total doses of approximately 6.4 mg/kg of dihydroartemisinin (DHA) and 51.2 mg/kg of PQ. DP was dosed as 20/160 mg DHA/PQ per dose for patients weighing 5.1–10.4 kg, and 30/240 mg DHA/PQ per dose for those weighing 10.5–14.5 kg. All doses were administered by nurses in the study clinic as crushed tablets dispersed in approximately 5 mL water, followed by 150 mL reconstituted cow's milk (Nido®, Nestle Corporation), which contains approximately 5 g of fat, to ensure optimal absorption of PQ. (33) Women who were breastfeeding were asked to feed after dosing. The full dose was re-administered if vomiting occurred within 30 minutes after dosing. No additional antimalarials or known hepatic enzyme inhibitors/inducers were administered during the study, with the exception of TS and ART in some patients as described above.

Sample collection

Samples of 125–200 μL whole capillary blood were obtained by finger prick and collected in heparinized microtubes on day 0 (pre-first dose), and days 2, 3 (24 hours post-third dose), 7, 14, 21 and 28. In order to inform absorption kinetics, day 2 samples were obtained either immediately prior to the last dose of DP, or at various intervals for up to 6 h after administration of the last DP dose. Day 0 and day 28 samples were added in July and August 2008, respectively. The microtubes were centrifuged immediately at $2000 \times g$ for 10 minutes, and plasma transferred to cryovials that were kept in liquid nitrogen. After completion of the study, all samples were transferred on dry ice to the Department of Clinical Pharmacology, Bangkok, Thailand for drug quantification.

Sample analysis

Analysis for PQ was conducted using high-throughput liquid chromatography coupled to tandem mass spectrometry as described previously. (15) Triplicates of quality-control samples at each of three PQ concentration levels were used to ensure precision and accuracy during quantification. The coefficients of variation during this quantification were 4.81, 4.15, and 2.27% at 4.5, 20, and 400 ng/mL, respectively. This method provides a limit of detection of 0.375 ng/mL, with a lower limit of quantification of 1.50 ng/mL.

Population Pharmacokinetic Data Analysis

Dose amounts used in the analysis were those of the base (the labelled dose of piperazine tetraphosphate salt multiplied by 0.577). PQ capillary plasma concentrations that were below the lower limit of assay sensitivity ($n=23$; 1.8%) were omitted from the PK data set. Also omitted were two outlying concentrations that were 2-fold and 10-fold higher than concentrations that preceded them, without an intervening dose. The population PK analysis was carried out using nonlinear mixed-effects modelling, with NONMEM[®], Version 7.3.0 (Icon Development Solutions, Elliott City, MD) using first-order conditional estimation with interaction. (34) Plots were made using the program R, Version 2.12.1 (The R Foundation for Statistical Computing); PsN, Version 3.5, (35) was used for bootstrapping to obtain standard errors and 95% confidence intervals, and for numerical and visual predictive checks.

The general model building approach began with the simplest reasonable structural and statistical models, then tested for more complex structural models and alternative statistical models, and lastly, tested for the influence of covariates on the PK parameters. Throughout the analysis, the residual error was an exponential model (i.e., error was additive to log-transformed values of observations). GOF plots were used to evaluate interim and final models. Formal testing was performed, regardless of preliminary evaluations, for all covariates (except sex) on CL/F ; body weight on each volume of distribution term; and age, weight, breastfeeding and vomiting status on F .

Hypothesis testing during model development was based on the likelihood ratio test, which compares the OFV of full versus reduced models with degrees of freedom ($d.f.$) equal to the difference in the number of parameters. The statistical significance of OFV is based on its approximate χ^2 distribution. Formal covariate testing was done using (in order) singular

addition, stepwise addition, singular deletion, and stepwise deletion. A p -value of 0.005 ($\text{OFV} -7.88$ with 1 $d.f.$) was considered significant for the final step (stepwise deletion); otherwise a p -value of 0.05 ($\text{OFV} -3.84$ with 1 $d.f.$) was applied. A nonlinear (power) model was used for models of continuous covariates, and a multiplicative model for categorical covariates.

A visual predictive check of the final model was performed using a sample size of 1000, and a numerical predictive check with 1000 simulated data sets, using the actual data set (with 107 individuals) as the basis for the distribution of covariate values and study design. In addition, simulations with 1000 hypothetical individuals based on the final model, and including a correlation of age and weight seen in the actual data, were done to evaluate dosing based on both age and weight.

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Abbreviations

WHO	World Health Organization
ACT	artemisinin combination therapy
DP	dihydroartemisinin-piperaquine
PQ	piperaquine
PK	pharmacokinetics
AL	artemether/lumefantrine
EIR	entomological inoculation rate
TS	trimethoprim-sulfamethoxazole
DHA	dihydroartemisinin
ART	antiretroviral therapy
LC	liquid chromatography
MS	mass spectrometry

GOF	goodness of fit
OFV	objective function value
IIV	inter-individual variability
IOV	inter-occasion variability
CL	capillary plasma clearance
F	bioavailability
V₂	peripheral volume of distribution
WT	weight
t_{1/2}	half-life
PI	prediction interval
k_a	first-order rate constant of absorption
CI	confidence interval
CYP3A4	cytochrome P450 3A4

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Study Highlights

What is the current knowledge on the topic?

Piperaquine pharmacokinetics has been characterized in adults and children over two years of age, but not in younger children. With current piperaquine regimens that are based on weight alone, children have lower systemic exposure to piperaquine than adults and are at greater risk of recrudescence with acute treatment.

What question does this study address?

This study characterizes the population pharmacokinetics, including covariate effects, of piperaquine in children less than two years of age.

What this study add to our knowledge

Like older children, those less than two years of age generally have lower systemic exposure than older children and adults, especially if they have lower weights. In addition to weight, age of young children is an important determinant of piperaquine disposition, bioavailability, or both.

How this might change clinical pharmacology and therapeutics

Together with simulations of alternative regimens as well as other investigations, a reassessment of piperaquine dosing recommendations in young children is urgently needed.

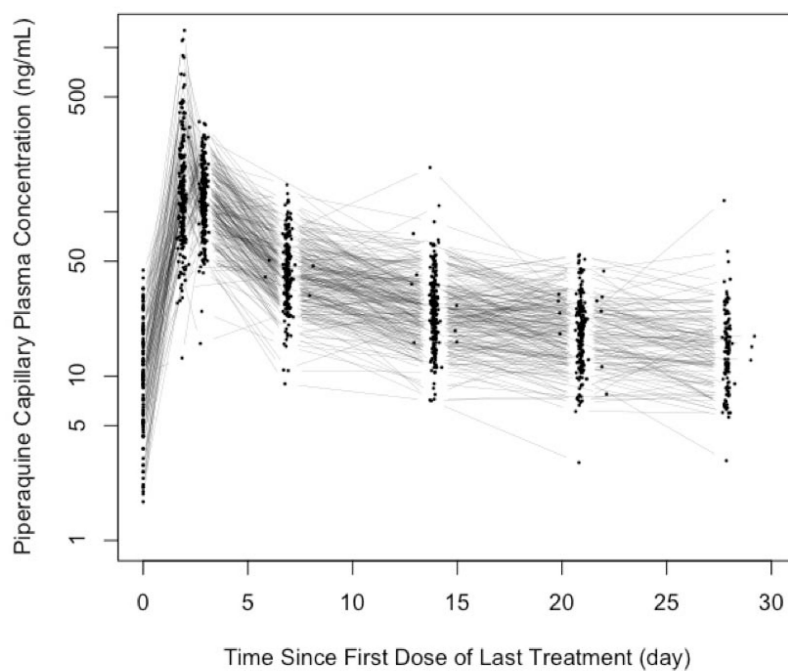


Figure 1. Piperazine capillary plasma concentration-time data in 107 children aged 6 months to 2 years after treatment with 3 daily doses of either 160 mg (children < 10.5 kg) or 240 mg (children ≥ 10.5 kg) piperazine phosphate.

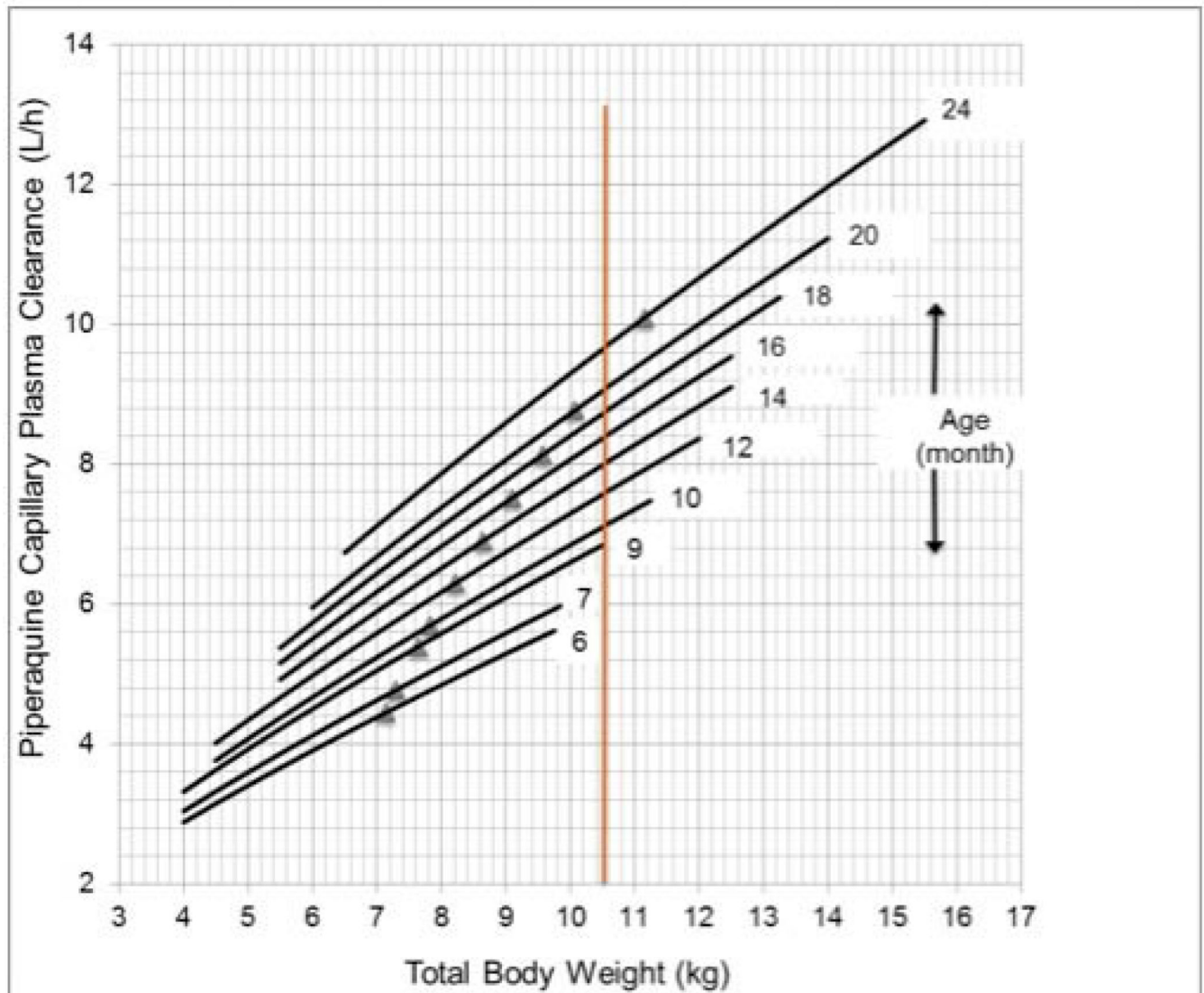


Figure 2.

Relationship of age and body weight with piperazine capillary plasma CL/F . Triangles represent the average weight and CL/F for each age group. With current doses based on whether body weight is above or below 10.5 kg (orange vertical line), those at greatest risk of low exposure are children between 1–2 years of age with lower weights.

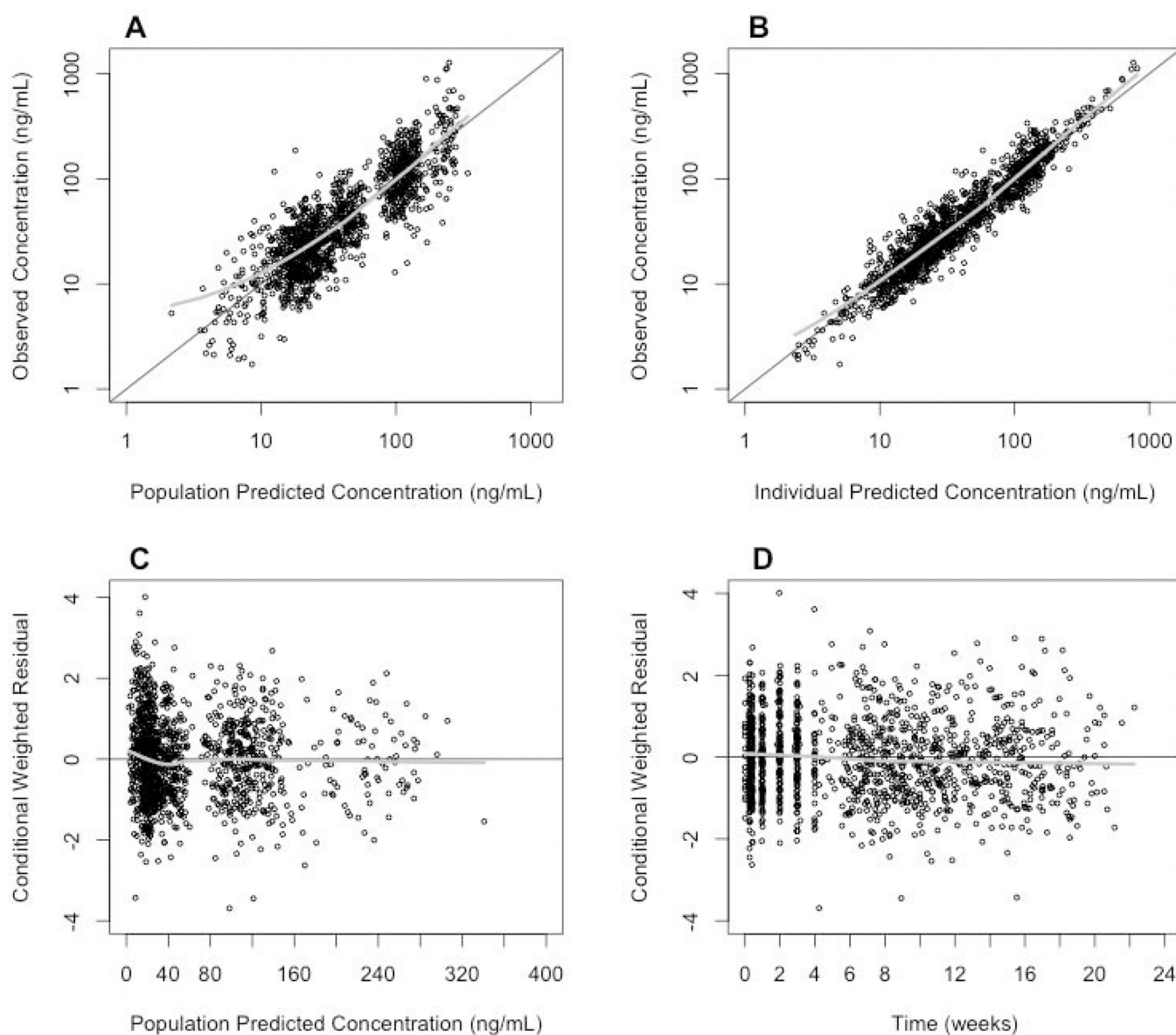


Figure 3.

Goodness of fit plots for the final population PK model of piperazine in children, showing population predictions (A) and individual predictions (B) versus observations, and population predictions (C) and time (D) versus conditional weighted residual. All conditional weighted residuals are within the range -4 to 4 . The thicker grey lines are smooths of the data; the narrow black lines are lines of unity (top panels) or weighted residuals of 0 (bottom panels).

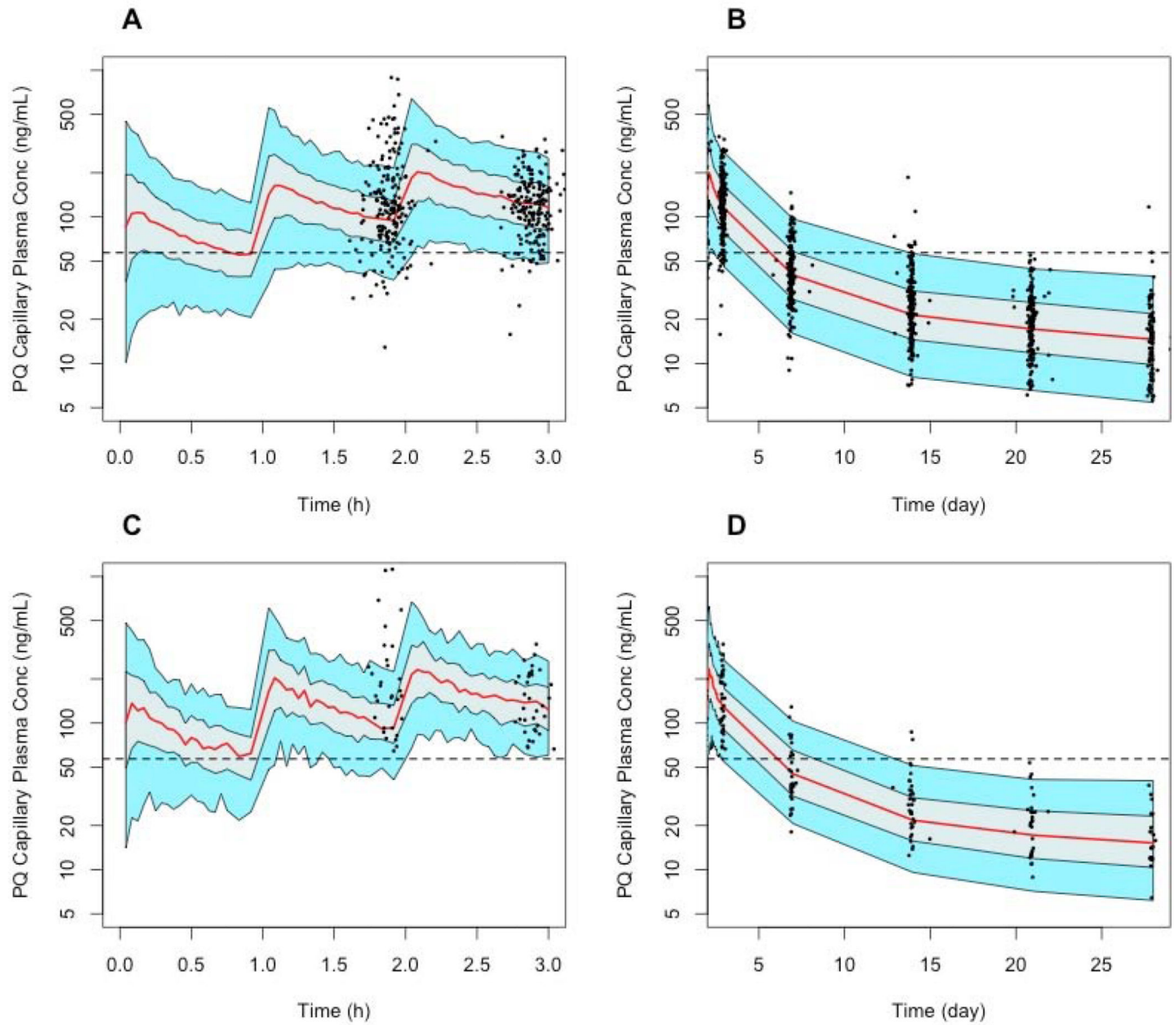


Figure 4.

Visual posterior predictive checks showing predictions of median (middle line), 90% confidence interval (outer bounds), and 50% confidence interval (inner shaded area) of capillary plasma concentrations for population PK model of piperazine versus time since first dose of last treatment in children, by dose: 160 mg every day \times 3; first 3 days (A), 160 mg every day \times 3; days 4–28 (B), 240 mg every day \times 3; first 3 days (C), and 240 mg every day \times 3; days 4–28 (D).

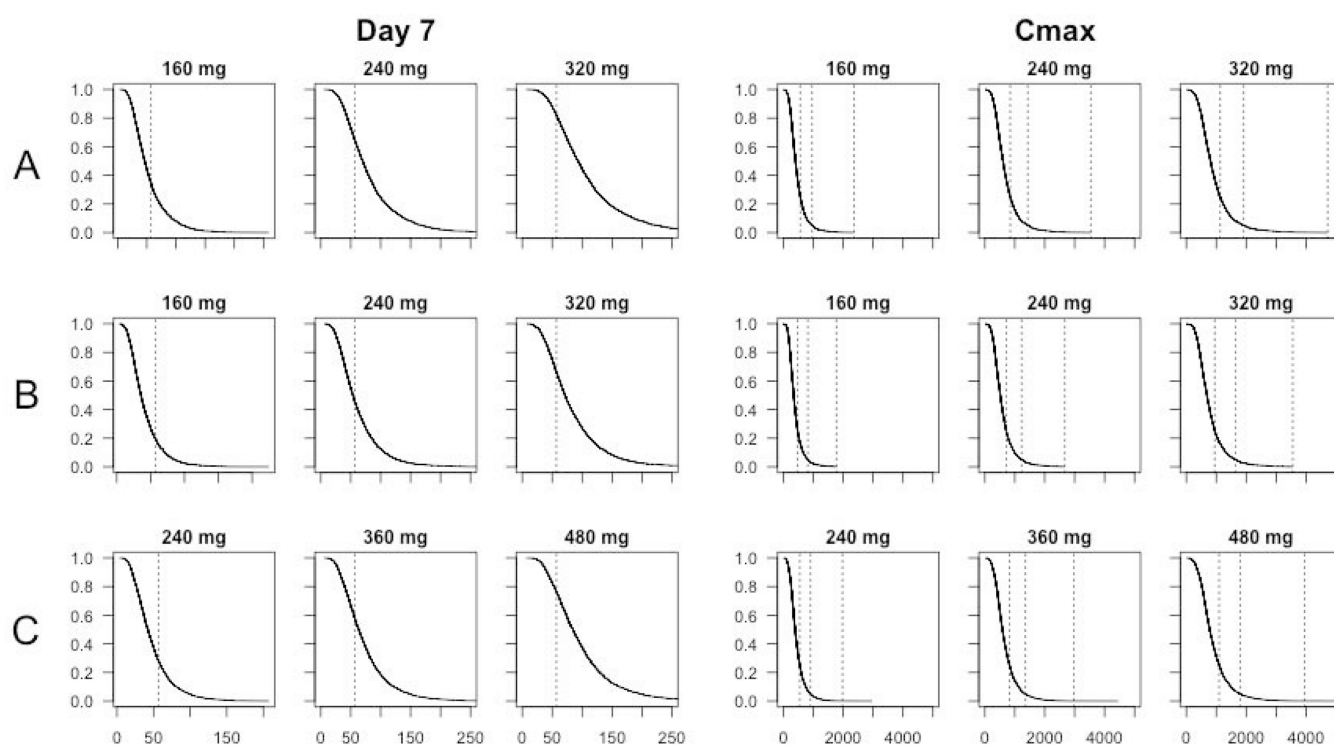


Figure 5.

Predicted percentage of children (y-axes) with a given piperaquine capillary plasma concentration (ng/mL; x-axes) on day 7, and with a given maximum concentration (C_{\max}) in each of three groups, children 6 months to 1 year old weighing less than 10.5 kg (A), children 1 to 2 years old weighing less than 10.5 kg (B), and children 1 to 2 years old weighing 10.5 kg or more (C). The vertical dashed lines for day 7 indicate the putative target of 57 ng/mL. The vertical dashed lines for C_{\max} indicate (going from left to right) the 75th percentile, the 95th percentiles and the largest value predicted in the 1000 children simulated.

Table 1

Parameter estimates for final population pharmacokinetic model of piperazine in children aged 6 months to 2 years

Parameter	Estimate	SE (%) ^c	95% CI ^d	
Structural Parameters				
$CL/F(L/h)^a$	6.34	6	5.54	7.04
Age effect on CL^a	0.35	41	0.06	0.67
$Q_2/F(L/h)^a$	10.9	6	9.6	12.2
$Q_3/F(L/h)^a$	49.4	32	27.5	98.7
$V_c/F(L/8.36\text{ kg})$	138	29	67	239
$V_2/F(L/8.36\text{ kg})$	4036	8	3459	4649
$V_3/F(L/8.36\text{ kg})$	700	10	561	832
$k_a\text{ (h}^{-1}\text{)}$	0.274	35	0.155	0.536
Secondary Descriptors ^b				
$Vd_{ss}/F(L/8.36\text{ kg})$	5420	2.2	5190	5660
$t_{1/2\alpha}\text{ (h)}$	1.54	9.3	1.25	1.82
$t_{1/2\beta}\text{ (h)}$	41.1	2.5	39.1	43.1
$t_{1/2\gamma}\text{ (day)}$	31.2	1.8	30.2	32.3
$AUC_{0-\infty}\text{ (}\mu\text{g}\cdot\text{h/mL)}$	71.3	1.5	67.2	72.6
$C_{day7}\text{(ng/mL)}$	42.5	2.4	39.4	45.9
$C_{max}\text{ (ng/mL)}$	162	0.7	147	178
Interindividual Variability (CV, %)				
CL/F	22	62	15	30
Q_2/F	14	97	6	27
Q_3/F	70	81	30	117
V_c/F	160	52	100	188
V_2/F	31	66	20	46
V_3/F	24	96	13	46
k_a	144	55	91	186
Interoccasion Variability (CV, %)				
CL	22	64	15	29
F	21	59	11	31
Residual error (CV, %)				
	61	17.3	59	63

Abbreviations: CL =clearance; F =relative bioavailability; Q_2 =intercompartmental clearance for central compartment and first peripheral compartment; Q_3 =intercompartmental clearance for central compartment and second peripheral compartment; V_c =volume of distribution of the central compartment; V_2 =volume of distribution of the first peripheral compartment; V_3 =volume of distribution of the second peripheral compartment; k_a =first-order rate constant of absorption; $t_{1/2\alpha}$ =initial half-life of the \ln concentration-time slope; $t_{1/2\beta}$ =middle half-life of the \ln

concentration-time slope; $t_{1/2\gamma}$ =terminal half-life of the ln concentration-time slope; C_{day7} =observed capillary plasma concentration on day 7; C_{max} =observed peak capillary plasma concentration

Footnotes:

^a – *clearance* models: $A \cdot (WT/8.36)^{0.75} \cdot B$ in which A is an estimated value (reported in table) and 8.36 is the approximately median weight (kg) for a child 12 months old; B is equal to 1 except for CL/F for which it is equal to $(AGE/12)$, with 0.35 being an estimated value;

^b – means of posterior estimates except for C_{day7} and C_{max} which are geometric means determined directly from data;

^c – bootstrap estimates;

^d – 95% confidence interval, from percentile bootstrap estimates

Table 2

Predicted percentage of children above the target 57 ng/mL on day 7 if given reference, 1.5× reference and 2× reference doses

Group	Actual	Simulation		
		Reference Dose*	1.5× Reference Dose	2× Reference Dose
6–12 mo	28.9	37.9	67.5	83.4
1–2 year, wt <10.5 kg	22.1	19.0	44.5	66.9
1–2 year, wt ≥10.5 kg	25.0	28.3	58.5	76.9

* The reference dose is that currently recommended: 160 mg × 3 if weight is < 10.5 kg and 240 mg × 3 if weight is ≥ 10.5 kg.

The absolute dose amounts are represented by the depth of shading, in the order lightest to darkest: 160 mg, 240 mg, 320 mg, 360 mg and 480 mg.